Results From RATIONALE 303: A Global Phase 3 Study of Tislelizumab (TIS) vs Docetaxel (TAX) as Second- or Third-Line Therapy for Patients With Locally Advanced or Metastatic NSCLC

Background: Anti-PD-1/L1 therapies have improved OS by 2-4 mo vs TAX in patients (pts) with advanced NSCLC who progressed after platinum regimens. TIS is an anti-PD-1 antibody engineered to minimize FcγR binding on macrophages, a mechanism of T-cell clearance and potential anti-PD-1 resistance.

Methods: RATIONALE 303 (BGB-A317-303; NCT03358875) compared efficacy and safety of TIS vs TAX as 2 or 3L therapy for pts with advanced NSCLC. Patients without oncogenic driver mutation who failed at least 1 prior systemic therapy including a platinum regimen were randomized 2:1 to receive TIS 200 mg IV Q3W (Arm A) or TAX 75 mg/m^2 IV Q3W (Arm B). Dual primary endpoints were OS in the ITT analysis set and OS in the PD-L1 high (≥25% TC) analysis set. A prespecified interim analysis (IA) was conducted after ≈426 deaths (76% of planned events); in the IA, formal OS superiority testing was conducted only in the ITT. The IA results are presented.

Results: Overall, 805 pts were randomized (n=535, TIS; n=270, TAX); demographics were generally balanced between arms. With a 19-mo median follow-up (441 OS events), median OS_{ITT} was significantly longer in Arm A vs B (17.2 vs 11.9 mo; HR=0.64 [95% CI: 0.53, 0.78]; *P*<.0001). OS benefit was also observed in the PD-L1 high analysis set (19.1 vs 11.9 mo; HR=0.52 [95% CI: 0.38, 0.71]) and across most subgroups including histology. In the ITT analysis set, PFS, ORR, and DoR were also improved in Arm A vs B (**Table**). Anemia (TIS) and alopecia (TAX) were the most commonly reported AEs (**Table**); pneumonia (TIS) and neutropenia (TAX) were the most common grade ≥3 AEs. AEs leading to death were 6.0% (TIS) and 4.3% (TAX); treatment-related AEs leading to death were 1.5% (TIS) and 1.6% (TAX).

Conclusions: RATIONALE 303 demonstrated that, as 2 or 3L therapy in pts with advanced NSCLC, TIS was tolerable and prolonged OS by 5-7 mo with improved PFS and ORR vs TAX regardless of histology or PD-L1 expression.

	ITT Analysis Set (N=805)			
	Arm A Tislelizumab (n=535)		**Arm B Docetaxel (n=270)**	
Efficacy				
Median OS, mo	**17.2**		**11.9**	
OS difference, mo	5.3			
HR (95% CI)[a]	0.64 (0.53, 0.78)			
P-value[a,b]	**<0.0001**			
Median PFS, mo	**4.1**		**2.6**	
PFS difference, mo	1.5			
HR (95% CI)[a]	0.64 (0.53, 0.76)			
P-value[a,b]	<0.0001[c]			
ORR, n (%)	**117 (21.9)**		**19 (7.0)**	
ORR difference, %	14.9			
OR (95% CI)	3.71 (2.24, 6.14)			
P-value[d]	<0.0001[c]			
Median DoR, mo (95% CI)	**13.5 (8.5, 21.8)**		**6.2 (2.1, 7.2)**	
Adverse event profile				
AEs occurring in ≥15% of patients in either arm, n (%)	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Anemia	152 (28.5)	18 (3.4)	112 (43.4)	16 (6.2)
Alanine aminotransferase increased	106 (19.9)	4 (0.7)	38 (14.7)	0
Cough	104 (19.5)	5 (0.9)	40 (15.5)	1 (0.4)
Aspartate aminotransferase increased	101 (18.9)	5 (0.9)	31 (12.0)	1 (0.4)
Appetite decreased	82 (15.4)	5 (0.9)	59 (22.9)	3 (1.2)
Weight decreased	81 (15.2)	4 (0.7)	26 (10.1)	0
Alopecia	5 (0.9)	0	122 (47.3)	2 (0.8)
Neutrophil count decreased	15 (2.8)	3 (0.6)	95 (36.8)	71 (27.5)
Neutropenia	9 (1.7)	3 (0.6)	81 (31.4)	72 (27.9)
White blood cell count decreased	20 (3.7)	1 (0.2)	74 (28.7)	47 (18.2)
Leukopenia	15 (2.8)	1 (0.2)	69 (26.7)	41 (15.9)
Asthenia	67 (12.5)	6 (1.1)	56 (21.7)	14 (5.4)
Constipation	65 (12.2)	0	42 (16.3)	0
Hypoalbuminemia	70 (13.1)	0	41 (15.9)	1 (0.4)
Nausea	59 (11.0)	0	41 (15.9)	1 (0.4)

Abbreviations: AE, adverse event; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; mo, months; NA, not available; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival.
[a]Stratified.
[b]One-sided log-rank test.
[c]Descriptive *P*-value.
[d]Cochran-Mantel-Haenszel.